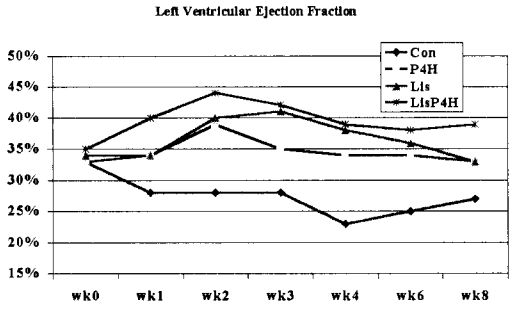
cal models of mammalian ventricular cells (dynamic Luo Rudy formulation) and early (myoblast) and late (myofiber) differentiated skeletal cells. The strands were either homogenous, or of mixed (half/half) cardiac and skeletal myofiber forms. They were used to explore coupling requirements and effects of action potential morphology on ventricular-skeletal interaction.
RESULTS: The action potential duration (APD) of skeletal cells is short (2.5 ms) and is the major limitation of skeletal-to-skeletal and skeletal-to-cardiac excitation. A high degree of intercellular coupling was required for skeletal cells to excite their downstream neighbors quickly enough, within 2.5 ms, prior to there own repolarization. The cardiac APD is long (178 ms) and there was a long length of time for cardiac cells to charge their downstream neighbor, before the charging cell repolarizes. Decreasing intercellular coupling increased the time necessary to charge adjoining cells. The ratio of intercellular coupling reduction to still allow cell-to-cell excitation in homogeneous strands was 45:5:1 for the ventricular, skeletal myoblast, and skeletal myofiber cell types, respectively. In mixed strands, the limiting factor in excitation was any instance that the skeletal cell was the source cell.
CONCLUSION: Skeletal cells need a very high degree of coupling to their neighbors and to ventricular myocardium for adequate cell-to-cell action potential flow. Gene therapy based interventions that prolong the skeletal APD such as introducing a slow inward calcium current, or use of cells with action potentials longer than 3 ms, would decrease this coupling requirement.

1204-145 Comparison of the Effects of Lisinopril and a Prolyl 4-Hydroxylase Inhibitor (FG041) on Left Ventricular Function After Acute Myocardial Infarction

John I. Nwogu, Maurice Bean, David L. Geenen, Jay Bagai, Ajanta De, Beth E. Reed, Mehdi Nafissi, Mitchell Brenner, Peter M. Buttrick, *University of Illinois at Chicago, Chicago, Illinois, Fibrogen INC, South San Francisco, California.*

Background: We have previously shown that proly 4- hydroxylase (P4H) inhibition by FG041, which specifically inhibits collagen biosynthesis when given after myocardial infarction (MI) decreases fibrosis, and improves left ventricular function (LVEF) and survival. ACE inhibitors decrease fibrosis and produce similar beneficial effects. It is unclear if ACE inhibitors and P4H inhibitors will produce similar and complementary effects on LV function post MI. **Method:** Rats who underwent left coronary artery ligation to produce MI were randomized to Lisinopril (Lis, n=13, at 15mg/kg QD) and FG041 (P4H, n=13,at 50mg/kg BID), Lisinopril and FG041 at same dose (LisP4H, n=10) and to vehicle (con, n=13). Echo was performed weekly for 4 weeks then biweekly till week 8 using a 15 mHz Linear probe. **Results:** At randomization, LV function and dimensions were similar in all groups. P4H and Lis produced similar improvement in LVEF compared to control (P<0.05 weeks 2-6, P =NS week 8). Combination therapy produced a more favorable effect on LVEF (see figure P<0.05 weeks 2-8 vs. con) and LV diastolic function (mitral inflow velocity 0.97m/s vs. 1.34m/s in con, p=0.028). **Conclusion:** Our data shows that FG041 and Lisinopril produced similar improvement in LVEF while combination therapy produced greater improvement in LV systolic and diastolic functions. Thus the two agents have comparable and complementary effects on LV function post MI.



POSTER SESSION

1205 Heart Failure: Prognostic Factors

Tuesday, March 19, 2002, 3:00 p.m.-5:00 p.m.
Georgia World Congress Center, Hall G
Presentation Hour: 3:00 p.m.-4:00 p.m.

1205-137 Atlas: Do Gender Differences Affect Outcome Results?

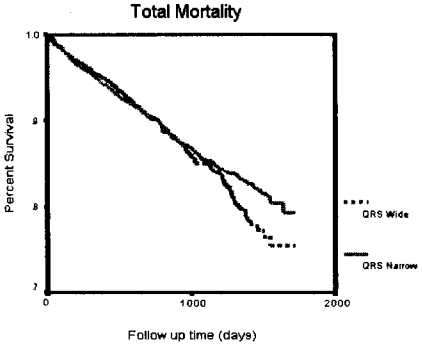
Margo M. Schleman, *AstraZeneca LP , Clinical Research, Wayne, Pennsylvania.*

Background: The Assessment of Treatment with Lisinopril (L) and Survival (ATLAS) trial found high dose L (32.5-35 mg) reduced combined endpoint of deaths and hospitalizations by 12% (p=0.0002) and trended to a reduction in all cause mortality by 8% (p=0.128). Women (n=648) comprised 20% of patient poulation. This retrospective analysis examined whether gender differences were present in demography, outcome results, or tolerabilty. Methods: A retrospective analysis of ATLAS data base was made based on gender and high and low dose L. Descriptive statistics were applied and an arbitrary cut off of 10% was used to identify differences. Results: Demography; Women had more history of hypertension than men (48% vs 19.4%) and men had more history of ischemic heart disease than women (67.5% vs 52%). Baseline systolic BP was higher in women (123.1 mmHg vs 119.4 mmHg). EF, NYHA class, DBP, and previous ACE inhibitor use were similar in both groups. Outcome results; All cause mortality hazard ratio (HR) for L (high dose :low dose) was neutral in women(HR=1.054, p=0.677) but trended positively in men (HR=0.891, p=0.053). Total mortality on either L dose in men was 1130 (45%) compared to 253 (39%) in women. HR for mortality plus hospitalizations was favorable in both women and men, HR=0.829, p=0.033 in women and HR=0.899, p=0.016 in men. Tolerability; High dose L was generally well tolerated in both men and women. Drop outs related to an Adverse Event (AE) occurred in 115 women (17.7%) and in 439 men (17.4%) with CHF and dyspnea the most frequently observed AEs (17%-28%). Increased cough occurred more frequently in women (high dose 14.8%, low dose 18.1%) than men (high dose 9.5%, low dose 11.9%) and sudden death was noted more frequently in men (high dose 15.1%, low dose 16%) than women (high dose11%, low dose 10.3%). Conclusion: High dose L was beneficial in men and women in reducing mortality plus hospitalizations. A strong trend (p=0.053) towards reducing mortality benefit in men was observed but not in women. A larger study in women is needed to definitively evaluate the response in mortality on high dose L. The overall results of ATLAS suggest uptitration of L is of benefit to both men and women.

1205-138 Prognostic Importance of a Wide QRS Complex in Asymptomatic Patients with Depressed Left Ventricular Function in Predicting Mortality

Sunny Srivastava, Amin Al-Ahmad, Munther K. Homoud, Mark S. Link, N.A. Mark Estes, III, Marvin A. Konstam, Paul J. Wang, Deeb N. Salem, *New England Medical Center, Boston, Massachusetts.*

Background: A wide QRS complex in patients with clinical heart failure is a potent predictor of death. However, the prognostic value of a wide QRS complex in asymptomatic patients with depressed left ventricular function is not known.
Methods: We performed a retrospective analysis on the 4228 patients enrolled in the Studies of Left Ventricular Dysfunction Prevention Trial. All patients had a left ventricular ejection fraction (LVEF) < 35% (mean 28.3%). The mean follow up was 32+/-15 months. QRS duration was noted to be > 120ms in 1186 patients and < 120ms in 2292 patients upon enrollment into the trial. A QRS duration > 120ms was evaluated as a predictor of all cause mortality univariate analysis with a Log-rank statistic. A Cox regression model was constructed for multivariate analysis with covariates that included LVEF, age, medication and medical history.
Results: A QRS duration > 120ms was not associated with an increased risk of death (univariate p = 0.31, multivariate p = 0.46).
Conclusions: In contrast to patients with clinical heart failure, in patients with asymptomatic left ventricular dysfunction QRS duration does not appear to be a predictor for mortality.



1205-140 Impact of South Asian (SA) Ethnicity On Presentation and Outcomes Following Hospitalization for Congestive Heart Failure (CHF)

Narendra Singh, Milan Gupta, Tuhina Biswas, Quak M. Nguyen, *Rouge Valley Health System-CHC site, Toronto, Ontario, Canada, William Osler Health Centre-Brampton campus, Brampton, Ontario, Canada.*

SA develop CAD at a younger age and have larger MI's compared to European Canadians (EU). We hypothesized that SA would therefore also develop CHF at a younger age. A retrospective review of 887 consecutive pts admitted between 1997-99 to 2 large community hospitals with a primary diagnosis of CHF was performed.
Results: CAD was the primary etiology of CHF in both groups (49 vs 48%). Pts with cardiac enzymes > 2 times normal were excluded. 99 (11%) of pts were SA and 728 (79%) were EU based on name analysis. 51% were males. SA were much younger (69.1 vs 75.1yrs, p=.000017), had more diabetes (57 vs 39% p<.001), were less likely smokers (24% vs 41% p<.01) had lower body mass index (24.4 vs 26.7kg/m2, p=.003), but similar hypercholesterolemia (27 vs 22%), hypertension (62 vs 59%), and family history of CAD (10 vs 9%). Prior history of CHF was similar in both groups (57 vs 58%) with the average ejection fraction also being similar (40 vs 42%).
On presentation, HR (98.1vs95.7 bpm p=0.4) and BP (139/82 vs 138/77, p=.02) trended higher in SA. Serum sodium was lower (135 vs 137mmol, p=.0002). Initial (150 vs 135mmol, p=0.1) and discharge creatinine (172 vs 144mmol, p=.014) were higher in SA. Most in-hospital complication rates were similar but SA had more ventricular arrhythmias/ cardiac arrest (10 vs 5%, p<.05) and less afib (15 vs 24% p<.05). Unadjusted mortality was similar (6 vs 11%, p=ns). Evidence-based drug therapies were used with similar frequency. Overall 66% received ACEI/ARB, 84% diuretic, 20% beta blockers, 17% spironolactone and 11% statins.
Conclusion Substantial differences at presentation are seen in SA pts hospitalized for

CHF. Despite being significantly younger, they presented with high risk features and had a higher in hospital complication rate although similar unadjusted mortality rate. This study suggests that pts of SA ethnicity are a high risk subset of the CHF population who may benefit from more aggressive therapeutic intervention at an earlier age.

1205-155 Mitral Regurgitation Is an Independent Risk Factor for Mortality In Patients With Heart Failure and Left Ventricular Systolic Dysfunction

Benjamin H. Trichon, G. Michael Felker, Linda K. Shaw, Christopher H. Cabell, Christopher M. O'Connor, *Duke Clinical Research Institute, Durham, North Carolina.*

Background: Mitral regurgitation (MR) is common in patients with heart failure (HF). However, mild MR accompanying left-ventricular (LV) dysfunction is often minimized in practice and the relation between the severity of MR and survival is not well characterized.

Methods: We assessed the incidence of MR in patients with HF (≥ NYHA II) and ejection fraction ≤40% undergoing cardiac catheterization between 1986 and 2000. MR was graded as mild (grade 1+/2+) or moderate/severe (grade 3+/4+).

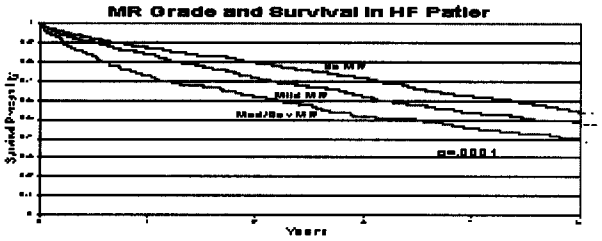
Patients with other valvular disease were excluded. Baseline characteristics of the population were defined. A multivariate Cox proportional hazards model was used to assess the independent effect of MR on survival.

Results: 2057 patients met study criteria. 1156 (56%) had MR identified. In 811 (70%), the MR was mild. Patients with MR were more likely to be older (63 vs. 60, p=0.001), female (43.4% vs. 28.9%, p=0.001), and have a gallop on exam (36.5% vs. 24.8%, p=0.001). Mean duration of follow-up = 3.4 years.

Compared to those without MR, patients with mild and moderate/severe MR had an 18% (HR=1.18, 1.03-1.36, p=0.01) and 53% (HR=1.53, 1.29-1.82, p<0.001) increased risk of death, respectively (GRAPH).

Conclusions:

MR is common in patients with HF and systolic dysfunction. There is an independent, progressive relation between MR severity and mortality. Studies are needed to investigate the effect of therapies (mitral valve repair or cardiac re-synchronization) on outcomes in patients with MR accompanying LV dysfunction.



1205-156 Prognosis of Women Compared With Men With Heart Failure and Acute Myocardial Infarction After Previous Revascularization

Predrag M. Mitrovic, Zorana Vasiljevic-Pokrajcic, Branislav Stefanovic, Jovan Perunicic, Gordana Matic, Nebojsa Radovanovic, Dubravka Rajic, *Cardiology Clinic, Institute for Cardiovascular Diseases, University Clinical Centre, Belgrade, Yugoslavia.*

Patients (pts) who have clinical evidence of congestive heart failure (CHF) after acute myocardial infarction (AMI) and previous coronary artery bypass grafting (CABG) have a poor prognosis. The aim of this prospective study was to analyze influence of gender on survival in pts with CHF and AMI after previous CABG. ***Methods:*** From April 1990 - August 2001 we studied 730 pts, who developed AMI after CABG, mean age 58.4±8.0 years, mainly men (80.8%). The pts with early perioperative AMI were excluded from the study. All pts were followed-up 12 years. The average time interval from CABS to AMI was 96.2 ± 16.0 months. The average number of grafts was 3.4 grafts/pts. There were 274/730 pts (37.5%) with signs of CHF. Clinical evidence of CHF was defined as at least two of the following: bibasilar rales, third heart sound or/and interstitial or alveolar edema on chest radiograph. All pts were divided in two groups: group I - 89/274 (32.5%) female with CHF and AMI after previous CABG and group II - 185/274 (67.5%) male with CHF and AMI after previous CABG. ***Results:*** There was no statistical difference in age, CABG-AMI interval, number of grafts/pts, AMI location, infarct size and risk factors for coronary artery disease. There were differences between groups in: previous angina pectoris (91% vs 56.8%, p<0.01), previous AMI (56.2% vs 31.3%, p<0.05), in-hospital mortality (15.7% vs 4.3%, p<0.05) and one-year mortality (40.4% vs 11.9%, p<0.01). ***Conclusion:*** This study suggests that female with signs of CHF and AMI after previous CABG had worse prognosis compared with male with CHF and AMI after previous CABG, specially in in-hospital and one-year period; the predictors of that prognosis were previous angina pectoris and previous AMI.

1205-157 The Incremental Prognostic Significance of Hyperuricemia In African Americans With Severe Heart Failure

Patricia A. Uber, Mandeep R. Mehra, Myung H. Park, Robert L. Scott, *Ochsner Cardiomyopathy and Heart Transplantation Center, New Orleans, Louisiana.*

Background: Compared with Caucasians (C), African Americans (AA)exhibit higher uric acid levels, a marker of free radical generation. We sought to determine the clinical impact of hyperuricemia in AA with severe Heart Failure (HF).**Methods:** 140 severe HF patients (52 ±11 years, ejection fraction 20 ±9%, 80% men, follow-up 12-72 months) awaiting heart transplantation were examined in order to evaluate the prognostic utility of baseline uric acid levels (≥7.5 versus < 7.5 mg/dl) at listing for transplantation, as a function of race. We analyzed detailed variables among the 106 C and 34 AA patients to assess variables predictive of HF hospitalizations or death in concert with hyperuricemia.**Results:** Baseline characteristics were similar in AA and C with regard to age, EF%, NYHA class, serum sodium, bilirubin, creatinine and HF medications. AA were more likely than C's to have hypertension (61% vs 40%, p =0.04), had a larger proportion of women (39% vs 13%, p = 0.007), and were more hyperuricemic (7.9 ± 2.1 vs 6.8 ± 2.0, p = 0.006). The results of actuarial event free survival at 3 years are shown in the table.

Group	African Americans	Caucasians	p value
Uric Acid ≥ 7.5mg/dl	60%	71%	0.04
Uric Acid < 7.5 mg/dl	86%	80%	ns
p value	0.03	ns	

Multivariable analysis demonstrated that hyperuricemia occurred independent of diuretic use, renal function, age and gender.**Conclusions:** Hyperuricemia, a marker of oxidative stress, is prevalent in AA and represents a discriminatory marker of poor clinical outcome in severe HF. This investigation provides insight into ethnic differences in oxidative stress as a critical determinant of prognosis in heart failure.

1205-158 Prediction of Morbidity and Mortality Following Myocardial Infarction

Kenneth Dickstein, Steven Snappin, The OPTIMAAL Trial Study Group, *Central Hospital in Rogaland, Stavanger, Norway.*

Introduction: It is important to choose the most appropriate endpoints in clinical trials evaluating an intervention on morbidity and mortality. The ability of these events to predict death impacts on patient selection and trial design.

Methods: 5477 patients with acute myocardial infarction and left ventricular dysfunction have been randomised to treatment with either captopril or losartan in the OPTIMAAL trial. During a mean follow-up period of 27 months there have been 584 patients with reinfarctions, 1561 patients with revascularisation (PTCA/CABG), 2670 patients with cardiovascular (CV) hospitalisations and 780 deaths.

Results: Baseline demographics contain powerful predictors for reinfarction, revascularisation or hospitalisation. The ability of selected variables to predict a heart failure (HF) hospitalisation are displayed in the table. The increases in risk of death associated with cardiovascular endpoints were: HF hospitalisation 746%, Reinfarction 502%, CV Hospitalisation 290%, Revascularisation -45% (P<0.001 in all cases).

Conclusion: Morbid events following complicated MI are predicted by selected baseline demographic variables. Death is predicted by these morbid endpoints. A heart failure hospitalisation was an especially powerful predictor for death. These data have implications for the choice of patients and endpoints in clinical trials seeking to assess the efficacy of an intervention on morbidity and mortality.

Increases in Risk of a Heart Failure Hospitalisation

Baseline Risk Factor		Clinical Status Prior to Randomization	
age (per year)	6%	tachycardia	83%
diabetes	62%	X-ray congestion	81%
atrial fibrillation	62%	IV diuretics	77%
prior diuretic	62%	pulmonary rales	60%
previous infarction	47%	EF<35%	52%
previous infarction	41%	gallop rhythm	48%
prior beta blocker	39%	Killip class (per class)	58%

P<0.001 in all cases

1205-159 Low Serum Total Cholesterol Is Associated With a Marked Increase in Mortality in Advanced Heart Failure

Tamara B. Horwich, Michele A. Hamilton, Robb MacLellan, Gregg C. Fonarow, *UCLA Medical Center, Los Angeles, California.*

Background: Although hypercholesterolemia is associated with CAD and cardiovascular mortality, the relationship between cholesterol and heart failure (HF) mortality is less certain.

Methods: Our study analyzed 1134 patients with advanced HF referred to a single center for transplant evaluation. The cohort was 75% men, etiology was 48% ischemic, and mean EF was 22%. Serum lipid panel was measured time of initial presentation. Patients were stratified into five groups based on quintiles of total cholesterol (TC) level.

Results: HF etiology, HTN, DM, and lipid-lowering therapy at time of referral were similar among the 5 TC groups. Patients with lower TC had significantly lower levels of LDL, HDL, triglycerides (TG), sodium and albumin. The lower TC quintiles had lower EF and cardiac output, but higher wedge pressures and increased likelihood of NYHA class IV. Decreased TC, LDL, HDL, and TG each predicted increased mortality (p=0.01) on univariate analysis. After adjustment for known predictors of HF mortality including BMI, elevated TC was an independent predictor of improved survival (0.996 RR for 1mg/dl increase), while LDL, HDL, and TG were not. See table for survival and relative risk of each TC quintile.

Conclusions: Low serum TC predicts HF outcomes independent of established mortality predictors, and thus represents a novel prognostic factor. Further investigations are necessary to determine whether a low TC level is merely a prognostic marker or is playing a causative role in HF mortality.